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Acute Profound Thrombocytopenia Following C7E3 Fab (Abciximab) Therapy: Case Reports, Review of the Literature and Implications for Therapy

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Platelets play a crucial role in the ischemic complications of percutaneous coronary procedures. The recent availability of C7E3 Fab (Abxiximab or ReoPro™), a chimeric monoclonal antibody Fab fragment directed against the platelet glycoprotein IIb/IIIa receptor, has reduced abrupt closure and other adverse events and lessened the need for revascularization procedures. As the use for this drug has increased, rare cases of severe thrombocytopenia have been revealed. From August 1995 to June 1997, 452 patients at Charleston Area Medical Center who underwent percutaneous coronary revascularization procedures and were treated with abciximab were evaluated for the development of severe thrombocytopenia (i.e., platelet count less than 20,000 within 48 hr of treatment). A review of published reports of severe thrombocytopenia was also reviewed. A review of published reports of abciximab-induced severe thrombocytopenia, as well as our three cases, reveals that: 1) the incidence is less than 0.7%; 2) the nadir platelet count (range 1,000–16,000) was noted within 2–31 hr after abciximab infusion; 3) the platelet count increases to greater than 100,000 within 12 days in all patients; 4) bleeding episodes were treated with platelet transfusion with an improvement in platelet count within 24 hr in all patients in whom they were given; and 5) in the one patient treated with γ globulin alone, no significant rise in platelet count was noted. Acute severe thrombocytopenia can occur after ReoPro™ administration. Its development is not predictable and may occur within 2 hr of administration. Thrombocytopenia, therefore, requires consideration in every patient treated with this drug. It appears prudent to obtain a platelet count 2 hr after initiating ReoPro™. If thrombocytopenia develops, then the drug can be stopped in a timely manner and platelet transfusion can be given. Am. J. Hematol. 61: 205–208, 1999. © 1999 Wiley-Liss, Inc.

Key words: C7E3 Fab therapy; thrombocytopenia; glycoprotein; platelets; abciximab; heparin

INTRODUCTION

Platelets place a crucial role in the ischemic complications of percutaneous coronary procedures [1]. The platelet membrane glycoprotein (GP) IIb/IIIa integren receptor is the final common pathway leading to platelet aggregation [2]. Local aggregation commonly occurs following atherosclerotic plaque rupture or other injury to the vascular wall [3]. When GP IIb/IIIa receptors are activated, fibrinogen and von Willebrand factor bind to the receptor with high affinity, cross-linking platelets and locking them to the vessel surface and to each other [2]. This process is crucial for arterial thrombus formation and consequent myocardial infarction, unstable angina, and abrupt closure following revascularization procedures [3]. The recent availability of abciximab (ReoPro™) a chimeric monoclonal antibody Fab fragment directed against the platelet glycoprotein IIB/IIIa receptor, has reduced abrupt closure and lessened the need for revascularization procedures [1]. This agent binds to the

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TABLE I. Incidence of Abciximab-Induced Thrombocytopenia in Three Large Clinical Trials (%)

Clinical Trial	Placebo	Abciximab
	Platelets ≤ 100,000	
EPIC[5]	3.5	5.2
EPILOG[6]	1.5	5.0
CAPTURE[7]	1.3	5.6
	Platelets ≤50,000	
EPIC[5]	0.7	1.6
EPILOG[6]	0.4	1.3
CAPTURE[7]	0.3	1.7

*Two patients had a platelet count of ≤20,000.

platelet GP IIb/IIIa receptor and inhibit s aggregation by preventing adhesive molecules with RGD sequence from binding to this platelet integrin [1]. Despite conferring clinical benefit, significant hemorrhagic complications and the need for blood product transfusion were increased in patients receiving abciximab [4,5]. Although retrospective analysis of some of the larger studies suggested that many of the bleeding events observed may have been associated with concomitant high-dose heparin therapy, a recent study utilizing weight-adjusted heparin dosing showed no increase in significant bleeding complications in patients receiving abciximab compared to those receiving placebo [6].

Thrombocytopenia ha been observed with the use of abciximab and may contribute to the hemorrhagic risk [4–9]. In the three largest clinical trials showing benefit of abciximab in unstable angina and/or myocardial infarction,[4–7] the incidence of thrombocytopenia (i.e., platelet count less than 50,000) ranged from 1.3–1.6% in patients treated with abciximab and heparin compared to 0.3–0.7% in those receiving placebo and heparin (see Table I). As the use of abciximab has increased, rare cases of severe thrombocytopenia (i.e., platelet count less than 20,000 have been reported [8,9].

We report the development of severe thrombocytopenia in three patients from our institution after they received abciximab and review the published literature.

METHODS AND RESULTS

Between August 1995 and June 1997, 452 patients at Charleston Area Medical Center, who underwent percutaneous coronary revascularization procedures, were treated with abciximab (C7E3 Fab, ReoPro™). Three patients developed acute profound thrombocytopenia, defined as a platelet count less than 20,000 occurring within 24–48 hr of initial treatment.

Pertinent features of these three patients are summarized in Table II. Two patients underwent balloon angioplasty and one underwent atherectomy. All received aspirin and heparin. All patients received a bolus dose of abciximab, and one received a continuous infusion. One patient had prior exposure to abciximab.

As shown in Table II, the nadir platelet counts ranged from 1,000 to 4,000 and occurred within 2–31 hr of initial bolus. Two patients (patients 1 and 3) developed mild groin hematomas and required no red cell or platelet transfusion. Patient 2 developed a groin, right forearm, and scrotal hematoma and hematemesis, and required 20 units of platelets and 2 units of red cells. The platelet count reached 100,000 or greater within 2–9 days after the initial bolus of abciximab.

DISCUSSION

Acute profound thrombocytopenia can occur after abciximab treatment. All three patients had normal baseline platelet counts before abciximab treatment, which makes immune or rheumatologic conditions or a bone marrow infiltration disorder unlikely causes. Splenomegaly was not detected in any patient. None of the patients had an abnormal prothrombin time, fibrinogen level, D-dimer titer, white blood cell count, hematocrit/hemoglobin level or peripheral blood smear (e.g., microangiopathic changes) making disseminated intravascular coagulation unlikely. Other than heparin, none of the patients received a medication (such as sulfa drugs, quinidine, or thiazide diuretics) likely to induce such severe thrombocytopenia. One patient had received ticlopidine, but no microangiopathic changes were noted on his blood smear. Heparin-platelet aggregtometry was performed in one patient and was negative. Although heparin as a cause of the thrombocytopenia cannot be excluded, temporally, the acute thrombocytopenia appears related to abciximab administration.

A summary of published reports of abciximab-induced severe thrombocytopenia is shown in Table III [8,9]. The incidence of severe thrombocytopenia is less than 1%. Only one patient had prior exposure to abciximab. The nadir platelet count (range: 1,000 to 16,000) was noted within 2–31 hr after initial abciximab infusion. The platelet count increased to over 100,000 within 12 days in all patients for whom postdischarge platelet counts were available. Heparin-induced platelet aggregation studies were negative in all eight patients in whom it was performed. Groin hematoma was the predominant bleeding complication. One patient had hematemesis and a scrotal hematoma in addition to a groin hematoma. Bleeding episodes were treated with platelet transfusion, with an improvement in platelet count within 24 hr in all patients in whom they were given. Two patients received intravenous γ globulin (IgG). In two patients, no transfusions were given.

The mechanism of the acute thrombocytopenia caused

TABLE II. Abciximab (ReoPro TM) Induced Severe Thrombocytopenia: Charleston Area Medical Center

Patient	Age (years) sex	Cardiac history	Procedure	First exposure	Admission platelet count	Nadir platelet count	Elapsed time between initial bolus and nadir platelet count (hours)	Elapsed time between initial bolus and platelet count >100,000 (days)	Bleeding complication	Transfusion requirement
1	48 M	CABG 1995, PTCA/stent LAD-2/96	Rotational Atherectomy	No	193,000	1,000	31	9	Groin hematoma	None
2	51 M	Unstable angina 6 months	PTCA/STENT RCA	Yes	258,000	4,000	2	2	Hematoma of groin, forearm and scrotum; hematemesis	Two units Packed red blood cells; 20 units of platelets
3	55 M	Unstable angina Inferior wall MI 2/97	PTCA	Yes	172,000	2,000	12	5	Groin hematoma	None

by abciximab is not well understood. Binding of abciximab to the GP IIb/IIIa platelet receptor produces a conformation change resulting in the expression of new epitopes, termed ligand-inducing binding sites. Endogenous antibodies targeted to these binding sites would cause platelet actuation or platelet-platelet interaction and result in consumption or removal of the platelets from the circulation. Thrombocytopenia would be the final result. Bednar et al. [10] have found such IgG antibody which binds to the above receptor in the presence of an experimental GP IIb/III a receptor antagonist and caused thrombocytopenia in chimpanzees and humans. Because abciximab has no F_c portion [1], it is unlikely that acute platelet removal and subsequent thrombocytopenia would be due to binding of the antibody to the F_c receptors of macrophages in the reticuloendothelial system. Pseudothrombocytopenia due to EDTA-dependent in vitro platelet clumping has been reported with abciximab treatment [11]. The pseudothrombocytopenia may also be due to antibodies that react with neoepitope on GP IIb/IIIa induced by a combination of abciximab Fab binding and strong divalent cation chelation.

In conclusion, analysis of our cases and those in the literature supports the following protocol for evaluation and management of abciximab-induced thrombocytopenia: 1) monitor the platelet count prior to abciximab treatment and 2–4 hr and 24 hr after treatment is started; 2) if the 2-hr post-treatment platelet count decreases to less than 100,000 or 25% from the pretreatment platelet count decreases to less than 100,000 or 25% from the pretreatment platelet count, the CBC should be checked more frequently; 3) draw platelet counts in separate tubes (one being citrated) to rule out pseudothrombocytopenia due to platelet clumping. A prothombin time, activated partial thromboplastin time, plasma fibrinogen, and D-dimer titer should be performed to exclud disseminated intravascular coagulation; 4) if thrombocytopenia is verified, the abciximab should be discontinued immediately; 5) platelet transfusion should be given if active bleeding is present. Although the practice of prophylactic platelet transfusion in antibody-mediated severe thrombocytopenia is controversial, it seems reasonable to give platelets prophylactically because transfusions have been effective in immediately raising the platelet count to safer levels in most case reports and because it may take longer than one week for spontaneous recovery of the platelet count (especially to >100,000) to occur; 6) intravenous IgG can be considered in addition to platelet transfusion, but is therapeutic effect is unknown. In the one patient in the reported literature treated with intravenous IgG alone, no significant rise in platelet count was noted [9]; 7) discontinue other possible offending medications such as heparin, quinidine, or sulfa.

TABLE III. Abciximab-induced Acute Thrombocytopenia: Summary of Published Studies

Author	Incidence	Age (years) gender	Nadir platelet	Elapsed time between initial bolus and nadir platelet count (hours)	Elapsed time between initial bolus and platelet count >100,00 (days)	First exposure	Bleeding complications	Transfusions
Kereiakes et al.[9]	4 of 575 (0.6%)	42 M	1,000	7	>3	Yes	Forearm hematoma	IV IgG alone
		64 M	12,000	18	3	Yes	Groin hematoma	8 units of platelets, IV IgG 500 mg/kg daily ×2
		70 M	11,000	12	3	Yes	Groin hematoma	8 units of platelets
		59 M	2,000	18	1	Yes	Groin hematoma	6 units of platelets
Berkowitz et al.[8]	4 of 744 (0.53%)	49 M	10,000	11	2.7	Yes	None	6 units of platelets
		53 M	16,000	11	12 (platelets 246,000)	Yes	Groin hematoma	12 units of platelets
		83 M	7,000	21	10 (platelets 185,000)	Yes	None	6 units of platelets
		62 M	1,000	21	6 (platelets 157,000)	Yes	None	Pheresed platelets
Present Study (Current Study)	3 of 452 (0.66%)	48 M	1,000	31	9	No	Groin hematoma	None
		51 M	4,000	2	2	Yes	Groin, scrotal, forearm hematoma; hematemesis	2 units red cells, 20 units platelets
		55 M	2,000	12	5	Yes	Groin hematoma	None

*Three more patients had thrombocytopenia after first exposure of abciximab. One patient had a platelet nadir of 6,000 and two each had a nadir count of 20,000. No other clinical details described. These three patients are not included in the overall estimate of the incidence of abciximab-induced thrombocytopenia.

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